APPENDIX

Fee Sheet

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USP 6,324,475 (Hayes)

Prudhomme (1998)

Mergler (1992)

Sobel (2000)

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Hirsch

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[54] **CHEMOSENSORY OLFACTORY ASSAY FOR SOMATIZATION DISORDERS**

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[62] Division of Ser. No. 229,059, Apr. 18, 1994, Pat. No. 5,380,765, which is a continuation of Ser. No. 954,882, Sep. 30, 1992, abandoned.

[51] Int. Cl.[6] A61K 31/045

[52] U.S. Cl. 514/730

[58] Field of Search 514/730

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[57] **ABSTRACT**

The invention provides a method for diagnosing a somatization disorder in a patient. The method involves administering to the patient a plurality of concentrations of the chemosensory agent 3-methyl-5-phenyl-3-pentanol, identifying at least a 5 decimel change in the threshold amount of the chemosensory agent detected by the patient, and correlating the change in detection of the chemosensory agent with at least one psychiatric disorder.

2 Claims, No Drawings

CHEMOSENSORY OLFACTORY ASSAY FOR SOMATIZATION DISORDERS

This is a division of application Ser. No. 08/229,059, filed Apr. 18, 1994, now U.S. Pat. No. 5,380,765, which is a continuation of application Ser. No. 07/954,882, filed Sep. 30, 1992, now abandoned, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

The ability to smell and, in part, the ability to taste is regulated by the olfactory nerve system. The olfactory nerve system is complex and interconnected with several systems in the brain. Olfactory receptors located in the nose are specialized bipolar neurons with cilia protruding into the mucous covering the epithelium. The axons of the bipolar neurons are packed into bundles that form connections in the olfactory bulb in the brain. The olfactory bulbs contain a rich supply of neurotransmitters and neuromodulators. Neuromodulators include thyrotropin releasing hormone, substance P, enkephalin, dopamine, glutamate, and aspartate. The neurotransmitters include serotonin, acetylcholine and noradrenaline which are delivered to the bulbs from cell bodies in other brain regions and are formed within the bulbs in the terminal projections only. Central olfactory projections from the bulb interconnect the bulb to other areas of the brain, including the hippocampus, the hypothalamus, and the pyriform lobe.

There is an anatomical and biochemical connection between the olfactory system and the limbic system in the brain. The limbic system includes the hippocampus and amygdala region, and is known as the emotional center of the brain. The limbic regions have many synaptic contacts with olfactory bulbs. Many of the limbic structures and the olfactory bulbs are reciprocally interconnected in loop pathways that may be involved in the regulation of brain emotional output.

There are several known disorders of taste and smell which affect the function of the olfactory system and which present major problems for the patient. Chemosensory dysfunctions are usually described by the following terms: ageusia (absence of taste), hypogeusia, (diminished sensitivity of taste), dysgensia (distortion of normal taste), anosmia (absence of smell), hyposmia (diminished sense of smell), and dysosmia (distortion of normal smell). These disorders cause modification of food choices and dietary habits, alter digestion, and the ability to detect noxious gases and poisons. Overall, chemosensory disorders are chronic problems that can reduce enjoyment and quality of life.

It is also known that neurological disorders involving damage to the brain can also include a chemosensory dysfunction. For example, patients suffering from Alzheimer's disease show a marked impairment in smell identification which may be associated with senile plaques, neurofibrillary tangles, and reduced cholinergic activity in the olfactory bulb.

SUMMARY OF THE INVENTION

The invention provides a method for diagnosing psychiatric disorder in a patient by administering a plurality of concentrations of a chemosensory agent, identifying at least a 5 decismel change in the threshold amount of at least one chemosensory agent detected by the patient and correlating that change with a diagnosis of at least one psychiatric disorder. Patients, particularly those presenting with a chemosensory dysfunction, can be tested with various olfactory or gustatory chemosensory agents and the threshold level of detection of those agents by the patient identified. Once identified, the threshold level of detection by the patient of at least one chemosensory agent is compared with the normal threshold amount and at least a 5 decismel change in the threshold amount detected by the patient can indicate a chemosensory and a psychiatric disorder. This invention is based on my discovery that the change in the threshold level of detection of a particular chemosensory agent correlates with a psychiatric disorder which has been confirmed in independent behavioral diagnosis. In a preferred version, the chemosensory agent is PE-phenol and the psychiatric disorder is depression.

The invention also provides for a kit for diagnosing a psychiatric disorder including: at least one chemosensory agent present in increasing concentrations ranging from sub-threshold to suprathreshold amounts; optionally, a chart indicating the expected threshold amounts for each of the chemosensory agents for each age group and sex of patients; and a chart of psychiatric disorders wherein the chart correlates a psychiatric disorder with at least a 5 decismel change in the threshold amount of the chemosensory agent detected by the patient. The kit preferably contains at least 10 different concentrations of one or more chemosensory agents and a chart correlating detection level of several chemosensory agents with different psychiatric disorders as shown in Table V.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of diagnosing psychiatric disorders in a human patient who has a chemosensory dysfunction or disorder. Patients with a chemosensory dysfunction have an alteration in the ability to taste or smell at least one chemosensory agent. A chemosensory agent is a compound that can be detected by a human's sense of smell or taste. Chemosensory dysfunctions or disorders are usually described by the following terms: ageusia (absence of taste), hypogeusia, (diminished sensitivity of taste), dysgeusia (distortion of normal taste), anosmia (absence of smell), hyposmia (diminished sense of smell), and dysosmia (distortion of normal smell). Using the method of the invention, a chemosensory dysfunction in the detection of at least one chemosensory agent correlates with and can be used to confirm a known psychiatric diagnosis.

A patient is evaluated for a chemosensory dysfunction using standard chemosensory assays known to those of skill in the art. The patient's ability to detect the type and threshold amount of a chemosensory agent by the sense of taste or smell is measured. The preferred chemosensory assays include the Smell Identification Test™, the Accusens T™ Taste Test, and unilateral threshold tests. The unilateral threshold test can be conducted by standard methods and provides for olfactory testing with any number of chemosensory agents. The standards for unilateral threshold testing in decismels, including the threshold concentrations for the chemosensory agents, can be obtained from OlfactoLabs, El Cerrito, Calif.

The chemosensory agent can be administered to the patient by smelling or tasting. The ability to detect the chemosensory agent in the right and left nostrils is tested separately. Preferably, different concentrations of the chemosensory agent are randomly given to the patient along with samples that do not contain the chemosensory agent.

Preferably, the patient correctly identifies the chemosensory agent at a particular concentration at least three times before the patient is scored as having correctly detected the chemosensory agent at that concentration. The threshold level of detection is the minimum concentration of the chemosensory agent detected by the patient.

Suitable examples of olfactory chemosensory agents include trichloroethene, 1,2-dichloropropane, isobutyl isobutyrate, naphthalene, pyridine, 4-ethylphenol, 3-methyl-5-phenyl-3-pentanol (hereinafter "phenylethyl methylethyl carbinol" or "carbinol"), tetrahydrothiophene, isovaleric acid, trimethylamine, L-carvone, pentadecalactone, 1-pyrroline, 1,8-cineole, isobutyraldehyde, 16-androsten-3-one, thiophane, PE-phenol (p-ethylphenol), CA-phenone (α-chloro-acetophenone), as well as the chemosensory agents in the Smell Identification Test™. Suitable gustatory chemosensory agents include salt (NaCl), sucrose, hydrochloric acid (HCl), urea, and phenylthiocarbamide (PTC). The preferred chemosensory agent is PE-phenol.

The patient's threshold level for detecting a chemosensory agent is identified and compared to the known threshold values for the same sex and age group. If the test samples containing a chemosensory agent are obtained from a commercial source, such as OlfactoLabs, El Cerrito, Calif., the samples are already calibrated in decismels and no conversion from absolute threshold concentration to decismels is necessary. Alternatively, the normal threshold concentration can be determined by administering the same concentrations of the chemosensory agent to a control group of at least 25 humans, who do not have a chemosensory dysfunction, and calculating the mean threshold concentration detected by the group of 25 individuals. Another alternative is to refer to the known threshold value for the chemosensory agent that has been established previously and published by J. Amoore et al., *J. Appl. Toxicology*, 3:272 (1983). A range of about −50 to +60 decismels is administered to the patient. A change of at least 5 decismels (about a 2-fold concentration change) from the normal or expected value is considered significant and indicative of a chemosensory dysfunction.

Odor thresholds are expressed on the decismel scale. The decismel scale is constructed by setting the mean threshold concentration of a chemosensory agent detected by the control group of 20 year olds at the 0 value. A decismel is calculated by dividing the concentration of the chemosensory agent detected by the patient by the normal threshold concentration (using the published value or empirically determining the value) and then taking the logarithm of the quotient. The logarithm of the quotient is then multiplied by 20 to obtain the decismel value. Decismel values can be positive or negative. A positive decismel value indicates the patient is less sensitive to the chemosensory agent, i.e. has a higher threshold detection concentration. A negative decismel value indicates that the patient is more sensitive to the compound, i.e. has a lower threshold detection concentration. An increase in the threshold concentration value over the mean threshold concentration value of 2-fold, corresponds to 6 decismels (or ds).

The suggested thresholds for hyposmia are 30 ds and functional anosmia at 54 ds. A change of at least 5 ds from the normal or expected value was considered a significant change in the threshold level of detection of the compound. Suitable corrections can also be made for the age of the patient. The threshold increase with aging is about 6 ds between ages 20 and 40, and another 6 ds between 40 and 60.

The change in detection of sensitivity to at least one chemosensory agent is correlated with a known psychiatric diagnosis by reference to a chart, such as that provided in Table V. A change in detection of a chemosensory agent correlates with a particular psychiatric disorder. For example, at least a 5 ds decrease in threshold detection level of PE-phenol in the left nostril correlates with depression. The more severe the depression, the greater the decrease in the threshold detection level of PE-phenol.

Other psychiatric diagnoses can also correlate with a chemosensory dysfunction as follows: a decrease in the threshold detection level of PE-phenol with depression; an increase in the threshold detection level of thiophane detected in the right nostril and a decrease in the left nostril with obsessive-compulsive personality disorder; an increase in the threshold detection level for CA-phenone, pyridine, salt, and sucrose with a dependent personality disorder; a decrease in the threshold detection level of salt and sucrose with anti-social personality disorder; an increase in the threshold detection level detected of CA-phenone with atypical personality disorder; an increase in the threshold detection levels detected for pyridine and CA-phenone with a passive-aggressive personality disorder; an increase in the threshold detection level for carbinol with a somatization disorder; and an increase in the threshold detection level of CA-phenone and thiophane correlates with schizoid personality disorder.

Optionally, a psychiatric diagnosis of the patient can be confirmed by methods known to those of skill in the art. Those methods can include a psychiatric interview, or administration of one or more written psychological tests, or a combination of both. Suitable examples of written psychological tests include the Minnesota Multiphasic Personality Inventory I and II (MMPI-I and MMPI-II), the Millon Clinical Multiaxial Inventory II™ (MCMI-II), the Beck Depression Inventory™. The tests are administered and analyzed by methods known to those of skill in the art. Patients having a chemosensory dysfunction in the detection of at least one chemosensory agent can also be given at least one written psychological test to confirm the psychiatric diagnosis which can then be analyzed by standard methodologies known to those of skill in the art.

Alternatively, the chemosensory assay can be used to confirm a suspected psychiatric disorder. The suspected psychiatric diagnosis can be suggested from the results of a psychiatric interview or by administration of one or more written psychological tests, or both. The chemosensory assay can be administered to a patient suspected of having a psychiatric disorder and used to confirm the psychiatric disorder.

In the preferred method, the threshold detection level of PE-phenol in a patient is determined in both the left and right nostrils separately. At least 10 separate samples with different concentrations of PE-phenol ranging from subthreshold to suprathreshold (i.e., −50 decismels to +60 decismels) are intermixed with samples containing water only. The patient is asked to smell a water sample, followed by a PE-phenol sample at a particular concentration, or in reverse order. The exposure with the same concentration of PE-phenol is repeated at least three times. The patient preferably correctly identifies a sample of the PE-phenol at least three times before a score indicating detection is marked for that concentration. The minimum concentration detected by the patient is identified as the threshold level and, if necessary, this level can be converted to decismels using the normal known or expected threshold value for PE-phenol. A decrease of at least 5 ds in the threshold detection level is correlated with depression, and the greater the decrease in the threshold detection levels of the patient, the more severe

the depression. Optionally, the diagnosis of depression can be confirmed by administering one psychological test, preferably the Beck Depression Inventory™.

The invention is also directed to a kit for diagnosing a psychiatric disorder. The kit includes at least one chemosensory agent present in a variety of concentrations ranging from sub-threshold to suprathreshold amounts for that chemosensory agent. The normal or expected threshold concentration can be a known value published by Amoore et al., cited supra., or can be determined empirically by testing a group of normal individuals with a plurality of concentrations of the chemosensory agent and calculating the means threshold concentration. Alternatively, the concentrations of the chemosensory agent can be supplied already converted to decismels, as described previously. A subthreshold amount is a concentration of the chemosensory agent below the normal or expected threshold concentration for that chemosensory agent. A suprathreshold amount is a concentration of the chemosensory agent greater than the threshold amount. The kit preferably contains about 10–64 different concentrations of the chemosensory agent ranging from about −50 decismels to +60 decismels.

Suitable examples of chemosensory agents include one or more of the following compounds: trichloroethene, 1,2-dichloropropane, isobutyl isobutyrate, naphthalene, pyridine, 4-ethylphenol, phenylethyl methylethyl carbinol, tetrahydrothiophene, isovaleric acid, trimethylamine, L-carvone, pentadecalactone, 1-pyrroline, 1,8-cineole, isobutyraldehyde, 16-androsten-3-one, thiophene, PE-phenol, CA-phenone. Suitable gustatory chemosensory agents include salt (NaCl), sucrose, hydrochloric acid (HCl), urea, and phenylthiocarbamide (PTC). The preferred chemosensory agent is PE-phenol.

The kit can also optionally include a chart indicating the normal threshold concentration values for at least chemosensory agent. The threshold concentration of the chemosensory agent detected by the patient is compared to the normal or expected value on the chart. At least a 5 decismel change in the threshold level detected by the patient of a chemosensory agent can be identified and correlated with a psychiatric disorder or central or peripheral nerve dysfunction.

The kit also includes a chart correlating at least a 5 decismel change in the threshold detection of a chemosensory agent with a psychiatric disorder. The chart includes the following correlations between changes in threshold levels of the detection for chemosensory agents with psychiatric diagnoses: a decrease in the threshold detection level of PE-phenol with depression; an increase in the threshold detection level of thiophane detected in the right nostril and a decrease in the left nostril with obsessive-compulsive personality disorder; an increase in the threshold detection levels for CA-phenone, pyridine, salt, and sucrose with a dependent personality disorder; a decrease in the threshold detection level of salt and sucrose with anti-social personality disorder; an increase in the threshold detection level detected of CA-phenone with atypical personality disorder; an increase in the threshold detection levels detected for pyridine and CA-phenone with a passive-aggressive personality disorder; an increase in the threshold detection level for carbinol with a somatization disorder; and an increase in the threshold detection level of CA-phenone and thiophane with schizoid personality disorder.

The preferred kit contains 10 different concentrations of each of the following chemosensory agents: PE-phenol, thiophane, pyridine, CA-phenone, carbinol, salt, sucrose and phenothiocarbimide (PTC). The preferred kit also contains a chart showing the normal threshold concentration values for each of these chemosensory agents for each sex and age group and optionally indicating hyposmia, anosmia, and hyperosmia. The preferred kit also contains a chart, such as shown in Table V, correlating at least a 5 decismel change in the threshold level detected of a chemosensory agent with a psychiatric disorder.

EXAMPLE I

Forty-six consecutive patients presenting to the Smell and Taste Treatment and Research Foundation with chemosensory dysfunction were evaluated for olfactory and gustatory dysfunction as well as psychological dysfunction. The patients' mean age was 40 years with a slight majority being men (61%), n=28. Presenting chemosensory complaints include: hyposmia, hypogeusia 96% (44), dysgeusia 20% (9) and phantageusia 37% (17). These problems were associated with diverse etiologies, as shown in Table I.

TABLE I

ETIOLOGY OF CHEMOSENSORY DISORDER (n = 46)

	Patients	Percentage
Post-Traumatic	21	46%
Post-Infectious	16	35%
Allergic Rhinitis	12	26%
Polyposis	6	13%
Medication-Induced	2	4%
Other	20	43%

The patients underwent psychiatric and neurological histories and examinations. They completed extensive olfactory and gustatory tests including the Smell Identification Test™, unilateral threshold testing, including carbinol, PE phenol, PD lactone, cineole, thiophane, pyridine, and CA phenone, and the Accuscus T™ Taste Test (see Table II).

TABLE II

CHEMOSENSORY TESTS		
Gustatory	Unilateral Olfactory Threshold Tests	Olfactory
NaCl	Carbinol	UPSIT - Formal
Sucrose	PD Lactone	Pennsylvania
HCl	Cineole	Olfactory Test
Urea	Thiophane	
PTC	Pyridine	
	CA Phenone	

Written psychological testing including the Minnesota Multiphasic Personality Inventory II™ (MMPI-II), the Millon Clinical Multiaxial Inventory II™ (MCMI-II), and Beck Depression Inventory™.

The Smell Identification Test™ was obtained from Sensonics, Inc. of Haddenfield, N.J., and was conducted according to standard methodologies as described in the *Smell Identification Test™ Administration Manual*. Briefly, patients were tested for smell identification and sensitivity to 40 stimuli using scratch and sniff cards. Each subject rated the fragrance samples by scratching with a pencil included with the test cards, sniffing, and then identifying the odorant as one of four choices. A label could be repeatedly scratched as needed before moving to the next odorant and returning to previous odors was allowed.

The results of the patient's score on the Smell Identification Test™ were evaluated by reference to the established